REMARKS

Formal Matters

The Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Claim Rejections – 35 USC § 103

Claims 1, 5, 6 and 18-23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hsuih et al. (hereinafter "Hsuih," *J. Clin. Microbiol.* 34(3):501-507, 1996) and Wenz et al. (hereinafter "Wenz," U.S. Patent Application No. 2003/0119004) in view of Hannon (*Nature* 418:244-251, 2002). The Applicants respectfully submit that the claims are patentable over the cited art for at least the reasons provided below.

Hsuih describes using two hemiprobes to detect a hepatitis C virus (HCV) RNA whereby the two hemiprobes bind to the HCV RNA and are ligated to each other (page 503, Fig. 1), but fails to teach a target nucleic acid of less than about 30 nt in length. In addition, Hsuih does not teach or suggest a siRNA or shRNA.

Wenz describes a method for quantitating a target nucleic acid sequence in a sample by hybridizing two target-specific probes to the target nucleic sequence, ligating the probes, amplifying the ligated probes and detecting the amplification product (page 1, paragraphs [0005] to [0006]), but does not disclose a siRNA or shRNA. In addition, Wenz does not teach or suggest a target nucleic acid of less than about 30 nt in length.

Hannon teaches that siRNA and shRNA can be used to manipulate gene expression experimentally (page 250, first col., 3d full paragraph). Hannon teaches that siRNA are double-stranded RNAs of lengths of about 21-23 nucleotides in length (page 248, Fig. 4). Hannon fails to teach or suggest steps for performing an assay for the presence of siRNA or shRNA.

In maintaining the rejection, the Examiner acknowledges that the deficiency present in the teachings of Hsuih et al. and Wenz et al. is the lack of length limitations of the target nucleic acid specifically recited in the instant claims, namely "less than about 30 nt" or "not to exceed about 25 nt", which are characteristic of siRNAs (or shRNAs).

However, the Examiner asserts that since Harmon's review article teaches that siRNA are double-stranded RNAs of lengths of about 21-23 nucleotides in length, it would have been obvious to one of skill in the art to apply the direct quantitation of Hsuih with the clinical applicability of Wenz to the short siRNAs of Hannon to arrive at the present invention.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones,* 21 USPQ2d 1941 (Fed. Cir. 1992). Second, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 231 USPQ 375 (Fed. Cir. 1986). Finally, the prior art reference, or references when combined, must teach or suggest all the claim limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974). All three criteria must be met. If any one of these three criteria is not met, a *prima facie* case of obviousness has not been established.

The Applicants respectfully submit that the direct quantitation method as taught by Hsuih could not amplify small RNA molecules with their method and that an attempt to modify the teaching of Hsuih by combining it with the siRNA of Hannon would produce an inoperable invention. With regard to 103(a) rejections, the court has stated the following:

> If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

The method of Hsuih entails first isolating the target HCV RNA by annealing it to two capture probes in admixture with the amplifying hemiprobes. Both sets of probes are large DNA molecules that complement and hybridize to large stretches of RNA within the captured RNA. Sequences of the probes are given in Hsuih, Table 1, reproduced for convenience below:

TABLE 1. Sequences of PCR primers, capture probes, and hemiprobes

Probes (no. of nucleotides)[a]	Sequence (5′ to 3′)[b]
PCR primer 1 (18)	GTTAGCAGATACACAGAC (sense)
PCR primer 2 (18)	CAAGAGCAACTACACGAA (antisense)
PCR primer 3 (18)	TTCTCGATTAGGTTACTG (antisense)
Capture probe 1 (45)	Biotin-AAGAGCGTGAAGACAGTAGTTCCTCACAGGGGAGTGATTCATGGT
Capture probe 2 (45)	Biotin-AAGACCCAACACTACTCGGCTAGCAGTCTTGCGGGGGCACGCCCA
Hemiprobe 1 (51)	ACTCACCGGTTCCGCAGACCACTATGGCTCGTTGTCTCTGTGTATCTGCTAAC
Hemiprobe 2 (69)	**CAAGAGCAACTACACGAA***TTCTCGATTAGGTTACTG*CAGAGGACCCGGTCGTCCTGGCAATTCCGGTGT
Full probe (120)	**CAAGAGCAACTACACGAA***TTCTCGATTAGGTTACTGCA*GAGGACCCGGTCGTCCTGGCAATTCCGGTGTACTCACCGGTTCCG CAGACCACTATGGCTCGTTGTCTGTGTATCTGCTAAC

[a] PCR primer 1 and PCR primer 2 were used for the first PCR with ligated full probes, and PCR primer 1 and PCR primer 3 were used for the second PCR.
[b] Underscores indicate sequences complementary to the 5′-UTR of HCV, outlined letters indicate the binding regions for PCR primer 1, boldface letters indicate the binding region for PCR primer 2, and italic letters indicate the binding region for PCR primer 3.

First, the capture probes of Hsuih would complement most or all of a 20-mer, thereby blocking the site of hemiprobe hybridization. As such, the capture and hemiprobes taught by Hsuih could not simultaneously anneal to the target molecules of Hannon. Even if the capture RNA and 20-mer were separated (by heat, for example), the capture probes would still create a large contaminating background during subsequent amplification of the target sequence, due to the presence of additional target sequence not on the target molecule itself nor on the annealed hemiprobes.

Moreover, the hemiprobes of Hsuih are large (i.e., greater than 20 nucleotides). For a small RNA target, these hemiprobes would overlap when hybridized and thereby unavoidably prime each other. Hsuih does not suggest how their method can be used for small RNA targets such as those taught by Hannon, since the method of Hsuih was

intended for the isolation and interrogation of large viral RNA genome fragments from serum (Hsuih, Abstract).

As such, attempting to combine the direct quantitation method of Hsuih with target nucleotides of less than about 30 nt in length as claimed, with or without the clinical relevance of Wenz, would result in an inoperable invention, teaching away from the combination and substantiating the nonobviousness of the present disclosure.

Moreover, Wenz fails to provide sufficient guidance such that one of skill in the art could use the disclosure of Hannon to devise the instantly claimed invention. As discussed in the instant specification, one challenge of detecting a small (< 30 nt) nucleic acid is that the size of the target imposes limitations on what means can be used to amplify and detect it.

Wenz is (a) silent with regard to the size of the target sequence, (b) silent with regard to the length of the probes, and (c) silent with regard to methods of detection regarding any particular sized target sequence smaller than 77 bases in length (Table 2, page 23). Moreover, Wenz teaches that the total nucleic acid content of a target tissue or cell is reverse transcribed to produce cDNA, and that it is the cDNA product of reverse transcription which is annealed to target-specific probes (Figure 1; Examples, page 24, paragraph 232).

As such, Wenz not only fails to teach detecting a target nucleic acid of less than about 30 nt in length in a sample by contacting the sample with at least two ligation domains, but teaches the ordinarily skilled artisan that the best method when seeking to detect a small message would be to reverse transcribe the sample, so as to produce a larger and more abundant message to which the method can be applied. One of skill in the art, upon reading Wenz and Hannon and consulting Figure 1 and the Examples of Wenz, would reverse transcribe the siRNA of Hannon to make cDNA, amplifying with probes at least including primer sequences, thereby yielding a larger DNA product to

which the target-specific probes of Wenz would then be annealed. This is not what is claimed. Since the method of Hsuih is unsuitable for the detection of a small nucleic acid, as established above, this deficiency would not be cured by consulting Hsuih.

Wenz must be read in its entirety for all that it teaches, especially with regard to treatment of the sample, i.e. amplification. The courts prohibit hindsight reconstruction of a different invention by cherry-picking particular elements of the prior art reference, and making them work together in a manner that is different from what the reference intends. The clear teaching of Wenz includes the amplification of target nucleic acids prior to other steps, and such cannot be applied to a small (< 30 nt) nucleic acid without divergence from the method disclosed in the present application.

It is insufficient that the prior art assertedly disclosed the components of RNA detection, clinical relevance, and RNAi, either separately or in combination; there must be some teaching, suggestion, or incentive to make the particular combination made by the inventor. Northern Telecom, Inc. v. Datapoint Corp. 15 USPQ2d 1321 (Fed. Cir. 1990), cert. denied, 498 U.S. 920 (1990).

In summary, Hsuih combined with Hannon results in a non-operable invention, which deficiency is not cured by Wenz, and Wenz combined with Hannon guides one away from the present invention, taken separately or together with Hsuih. As such, the combined references teach away from the instant claims. Accordingly, the claims are patentable over Hsuih and Wenz in view of Hannon.

In light of the foregoing discussion, the Applicants believe this rejection to have been adequately addressed. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim Rejections – 35 USC § 103

Claims 32-38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hsuih et al. (hereinafter "Hsuih," *J. Clin. Microbiol.* 34(3):501-507, 1996) and Wenz et al. (hereinafter "Wenz," U.S. Patent Application No. 2003/0119004) in view of Hannon (*Nature* 418:244-251, 2002). The Applicants respectfully submit that the claims are patentable over the cited art for at least the reasons provided below.

Claims 32-38 depend from Claims 1 and 18, discussed above.

In making this rejection, the Examiner asserts that the size limitations recited in the rejected claims are disclosed by Hannon.

As established above, Hsuih combined with Hannon results in a non-operable invention, which deficiency is not cured by Wenz, and Wenz combined with Hannon guides one away from the present invention, taken separately or together with Hsuih. As such, the combined references teach away from the instant claims. Accordingly, the claims are patentable over Hsuih and Wenz in view of Hannon.

The Applicants believe this rejection to have been adequately addressed. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number NATH-003.

Respectfully submitted,

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Date: April 9, 2007

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